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Amendments to the Drawings:

The attached sheet of drawings includes changes to Fig. 5. This sheet, which includes Fig. 5 replaces the original sheet including Fig. 5.

The amendment includes changing the label "I5Ia" to "5a" as requested by the Examiner. No new matter is added.

Attachment: Replacement Sheet

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Appl. No. 10/626,493
Amdt. dated November 15, 2006
Reply to Office Action of June 16, 2006,

REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

Claims 1-35 are pending and claims 36-53 are cancelled. Claims 1, 2, 13, 16, 22, 24, 26, 28, 31, 32, 34, and 35 are amended. Support for the amendments to correct antecedent basis in the claims is the same as for the original claim. Support for the amendments to claims 1 22, 28 and 31 to provisio out nucleic acids as a species of affinity molecule can be found e.g., on page 14, paragraph 63. Support for the amendment to claim 24 clarifying that the samples to be compared are subject to different conditions can be found on page 12, paragraph 54. No new matter is introduced with this amendment.

II. ELECTION/RESTRICTION

Applicants acknowledge the telephone conversation with the Examiner on April 7, 2006, where a provisional election was made with traverse to prosecute the invention of Grou I. Applicants hereby affirm the election made with traverse to prosecute the invention of Group I (claims 1-35).

III. REPLACEMENT DRAWING

The Examiner has objected to figure 5 because the label "I5I-a" should be "5a." Applicants thank the Examiner for pointing this out and hereby submit a replacement drawing in which the label is corrected as suggested by the Examiner. No new matter is added.

In view of the replacement drawing, Applicants request that the objection be withdrawn.

IV. OBJECTION TO THE SPECIFICATION

The Examiner has objected to the specification because the brief description of the drawings does not include figures: 4a-4c, 5a-5c, 6a-6c, 7a-7c, 8a-8c, and 9a-9c.

Applicants have amended the brief description of the drawings to include a description of the subparts for each figure as requested. In light of the amendment, Applicants request that the objection be withdrawn.

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V. CLAIM OBJECTIONS

Claim 35 is objected to because it is missing a period. Applicants have amended the claim to correct the informality.

Claims 16, 26, and 32 are objected to for lack of the term "further" before the word comprising in line 1 of each claim. Applicants have amended the claims to correct the informality.

In light of the claims as currently amended, the Applicants request that the objections be withdrawn.

VI. 35 U.S.C. 112 SECOND PARAGRAPH

Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter the Applicant regards as the invention. Specifically, the Examiner has indicated multiple terms in the claims that are alleged to lack antecedent basis. In addition to the specific instances where terms lack antecedent basis cited by the Examiner, the Applicants have corrected the lack of antecedent basis throughout the claims. Other than the specific rejections discussed below, the Applicants have amended the claims to include the antecedent basis requested by the Examiner.

The Examiner alleges that claim 1 is indefinite because it is not clear whether the complex is interacting with the sample, or whether the sample comprises the complex. Applicants disagree with the Examiner, but in an effort to expedite prosecution, have amended the term "for" in line 2 of the claim to recite "in" thereby clarifying that the sample comprises the complex as interpreted by the Examiner.

The Examiner alleges that "the successive elution washes" in line 11 of claim 1 lacks antecedent basis. Applicants have amended the claim to delete "successive," thereby clarifying that the second component is measured in the elution washes referred to in step (b), as such, no antecedent basis is required for the phrase in line 11.

The Examiner alleges that "the concentration" in step (b) of claim 1 lacks antecedent basis. Applicants have amended step (b) to provide antecedent basis for

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"concentration" and to clarify that concentration refers to the first solute in the elution washes that form a sequential gradient of the solute (e.g. increasing stringency).

The Examiner alleges that "the immobilized complex" in step (b) of claim 1 lacks antecedent support and it is unclear to what the immobilized complex refers. Applicants disagree and submit that it is clear that the immobilized complex refers to the "multicomponent biological complex from the sample immobilized on a solid support" in step (a). However, in an effort to expedite prosecution of the claims, Applicants have amended the claim to recite that the immobilized complex is "the immobilized multicomponent biological complex."

The Examiner alleges that claim 1 is indefinite for reciting "measurements" in line 12-13, but the claim only refers to a single measurement. Applicants disagree. The profile is comprised of the measurements for a second component in each elution wash. It is clear from the claim that a sequence of washes are performed and that each wash is measured for the second component. However, in an effort to expedite prosecution of the application, Applicants have amended step (c) to clarify that each of the elution washes are measured for the second component.

The Examiner alleges that the phrase "the group" in claim 2 lacks antecedent basis. Applicants disagree. As the Examiner will recognize, claim 2 recites a Markush group, and the format of "...selected from the group consisting of..." is proper. *See*, MPEP §803.02.

Examiner alleges that "the biospecific capture reagent" in claim 13 lacks antecedent basis. Applicants have amended the claim to clarify that what is referred to is the "biospecific affinity agent."

The Examiner alleges that claim 21 is indefinite for reciting "whereby the profile further comprises measurement of the complex." The Examiner interprets this measurement as referring to the same measurement in line 11 of claim 1.

Applicants disagree with the Examiner's assertion. Specifically, Applicants contend that the claim is not vague or indefinite and that it is clear that the measurements refer to "components of the complex still immobilized on the support through the biospecific affinity molecule." Thus, the measurements in claim 1 are of the components that are eluted in the washes, while the measurements in claim 21 are directed toward those components that are not

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eluted in the washes, but rather are still immobilized on the solid support through the biospecific affinity molecule.

With regard to claim 24, the Examiner alleges that the claim is ambiguous because the biological characteristic is a condition rather than a property of the subset. The Applicants disagree. However, in an effort to expedite prosecution fo the application, Applicants have amended the claim to clarify that the subsets of the sample differ in their biological characteristics based on either exposure or non-exposure to inhibitor RNA.

Applicants believe the claims as amended sufficiently address the Examiner's concerns, and respectfully request that the rejection be withdrawn.

VII. 35 U.S.C. 102(e)

Claims 1-6, 8, 11, 12, 14, 15, and 28 are rejected under 35 U.S.C. §102(e) as being anticipated by Church *et al.*, U.S. Pat. No. 6,548,021. With regard to independent claims 1 and 28, the Examiner alleges that the Applicants method for creating a profile of interactions between components of at least one multicomponent biological complex for a sample is taught by Church *et al.* Specifically, the Examiner alleges that Church *et al.*, teaches "assaying for the relative affinities for the recognition sites for a protein by binding them to chips or chromatography supports to which are complexed oligonucleotides and eluting them off in buffers of gradually increasing ionic strength." *See*, page 10 of the Office Action and col 23, lines 46-53 of Church *et al.*

Applicants disagree with the Examiner's assertion, because Church *et al.*, does not teach all of the elements of the invention as claimed. Specifically, independent claims 1 and 28 recite that the affinity molecule is not a nucleic acid. Support for this is found in the specification, which states that "[S]uitable affinity molecules include antibodies directed to one or more antigenic components present in the complex, receptors, enzymes, and in the cases where the multicomponent biological complex itself is an enzyme, substrates for the activity associated with the multicomponent biological complex. *See*, page 14, paragraph [63] of the specification. In contrast, Church *et al.*, teaches a method where the affinity molecule is a nucleic acid. *See*, page 10 of the Office Action; col. 23, lines 27-29 and col. 23, lines 46-53 of

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Church *et al.* Thus, Church *et al.*, does not anticipate claims 1 and 28, because Church *et al.*, does not teach all of the elements of the claims as presently recited.

In light of the above, the Applicants request that the Examiner withdraw the rejection.

Claims 2-6, 8, 11, 12, 14, and 15 depend either directly or indirectly from claim 1 and therefore include all of the limitations of independent claim 1. Therefore, the arguments presented above with regard to claim 1 are also applicable to the dependent claims. As such, the Applicants request that the Examiner withdraw the rejection.

VIII. 35 U.S.C. 103(a)

A. Claims 9, 10, 16-19, 21-27 and 29-35 are rejected as unpatentable over Church et al (U.S. Pat. No. 6,548,021).

Claims 9, 10, 16-19, 21-27 and 29-35 are rejected under 35 USC 103(a) as being unpatentable over Church *et al.*, U.S. Pat. No. 6, 548,021. The Examiner alleges that Church *et al.*, discloses the invention substantially as claimed (*see supra*). Specifically, the Examiner alleges that Church *et al.*, teaches an array of nucleic acid sequences that can be immobilized on a support and used for binding proteins for which it has affinity, and eluting off the proteins in buffers of gradually increasing ionic strength. *See*, page 12 of the Office Action.

As to independent claims 22 and 31, the Examiner alleges that the step of providing two sets of biological samples, each subset characterized by a different biological characteristic and creating a profile of interactions for each sample by washing an immobilized complex with a plurality of successive elution washes and comparing the profiles from the samples to detect differences in interaction between components in each subset is substantially disclosed by Church *et al.* See, page 14 of the Office Action. The Examiner alleges that Church *et al.*, teaches assaying for the relative affinities for the recognition sites for a protein by binding them to chips or chromatography supports to which are complexed oligonucleotides and eluting them off in buffers of gradually increasing ionic strength, or salt concentrations. *See*, page 14 of the Office Action and col. 23 lines 46-61 of Church *et al.*

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1. Burden of Proof in Establishing Prima Facie Obviousness

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the Examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." See *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained in more detail below, the Examiner has not established a proper *prima facie* case of obviousness because the cited references do not teach or suggest all of the elements of the invention as presently claimed.

2. Church *et al.*, does not teach or suggest that the biological affinity molecule is not a nucleic acid.

As discussed above with regard to the 102(e) rejection, Church *et al.*, does not teach all of the elements all of independent claim 1. Specifically, Church *et al.*, does not teach or suggest that the biological affinity molecule affinity molecule, through which the first component of the multicomponent biological complex is attached to the solid support, is not a nucleic acid.

Claims 9, 10, 16-19 and 21 depend either directly or indirectly from independent claim 1, and therefore include all of the limitations of claim 1. The Examiner has not established a proper *prima facie* case of obviousness with regard to claims 9, 10, 16-19 and 21 because Church *et al.*, does not teach or suggest all of the elements of the independent claim from which the rejected claims depend.

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This same argument is also applicable to independent claims 22 and 31, and to claims 23-27 and 29, which depend from claim 22 as well as claims 32-35 which depend from independent claim 31.

In view of the above, the Applicants respectfully request that the Examiner withdraw the rejection.

B. Claim 7 is rejected as unpatentable over Church *et al.*, (U.S. pat No 6, 548,021) in view of Beutler *et al.*, (U.S. Pat. No. 5,234,811).

The Examiner cites Church *et al.*, for the reasons cited *supra*. The Examiner, acknowledges that Church *et al.*, does not teach an embodiment where the nucleic acid is bound to the solid support after binding the complex.

The Examiner, however, cites Beutler *et al.*, as teaching that the probe/target hybrids may be selectively isolated on a solid matrix, as an alternative to immobilizing the probe nucleic acids on a solid support and using it to capture the target sequences from the solution. The Examiner alleges that it would have been obvious to one of skill in the art to allow binding of the double-stranded nucleic acid molecules to its target in Church *et al.*, before immobilizing the probe target hybrids to the solid support because Beutler *et al.*, teaches that probe/target hybrids may be selectively isolated on a solid matrix.

Applicants contend that the Examiner has not established a proper *prima facie* case of obviousness, because Church *et al.*, in view of Beutler *et al.*, does not teach all of the elements of claim 7. Specifically, claim 7, depends from claim 1 and therefore includes all of the limitations of claim 1. As discussed *supra*, Church *et al.*, does not teach or suggest that the biological affinity molecule is not a nucleic acid, and Beutler *et al.*, does not cure this defect.

In light of the above, the Applicants respectfully request that the Examiner withdraw the rejection.

C. Claims 13 and 20 are rejected as unpatentable over Church *et al.*, (U.S. Pat. No. 6,548,021) in view of Hutchens *et al.*, (U.S. Pat. No. 5,719,060).

Claims 13 and 20 are rejected as unpatentable over Church *et al.*, (U.S. Pat. No. 6,548,021) in view of Hutchens *et al.*, (U.S. Pat. No. 5,719,060).

The Examiner cites Church *et al.*, for the reasons discussed *supra*. The Examiner acknowledges, however, that Church *et al.*, does not teach the solid support is a SELDI probe.

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The Examiner cites Hutchens *et al.*, as teaching a SELDI probe as a solid support for immobilization of affinity capture probes having specific affinity for an analyte and that the SELDI probe provides the advantages of providing much more efficient and sensitive affinity mass spectrometry. *See*, page 20 of the Office Action; col. 11, lines 21-39 and col. 13, lines 40-60 of Hutchens *et al.*

Furthermore, the Examiner alleges that it would have been obvious to a skilled artisan to use a SELDI probe as the solid support because Church *et al.*, teach the use of solid supports in general for elution washes, and Hutchens *et al.*, teach that a SELDI probe may be used to immobilize affinity capture probes having specific affinity for an analyte and that the SELDI probe provides the advantages of providing much more efficient and sensitive affinity mass spectrometry.

Moreover, as to claim 20, the Examiner cites Hutchens *et al.*, as disclosing that the SELDI may be specifically SEND. *See*, page 21 of Office Action and col. 13, lines 40-44 of Hutchens *et al.*

Applicants contend that the Examiner has not established a proper *prima facie* case of obviousness, because Church *et al.*, in view of Hutchens *et al.*, does not teach all of the elements of claims 13 and 20. Specifically, claims 13 and 20 depend either directly or indirectly from claim 1, and therefore contain all of the limitations of the independent claim 1. As discussed above, Church *et al.*, does not teach or suggest all of the elements of claim 1, specifically, that the biological affinity molecule is not a nucleic acid molecule. Hutchens *et al.*, does not cure the defects of Church *et al.* Therefore, Church *et al.*, in view of Hutchens *et al.*, does not teach or suggest all of the elements of claims 13 and 20.

Furthermore, even if the claimed references did teach all of the elements of the claims, which the Applicants contest, the Examiner has not pointed to where in the references a skilled artisan would find a motivation to combine SELDI probe of Hutchens *et al.*, as a solid support in the methods of Church *et al.*, to arrive at the Applicants invention.

The Examiner bases the *prima facie* case on a skilled artisan recognizing the advantages of the SELDI probe as providing more efficient and sensitive affinity mass spectrometry. *See*, page 20 of the Office Action. However, Church et al., teaches that the

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complexes are eluted off the solid support (i.e. the SELDI probe) and detected in the eluant. As such, the increased efficiency and sensitivity provided by the SELDI probe would be of little use Therefore, one of skill in the art would not be motivated to use the SELDI probe of Hutchens *et al.*, as a solid support in the methods of Church *et al.*, to arrive at the Applicants invention in claims 13 and 20.

In light of the above, the Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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